What is claimed is:

1.   A method for continually or continuously measuring an analyte present in a biological system, said method comprising:

(a)   transdermally extracting the analyte from the biological system using a sampling system that is in operative contact with a skin or mucosal surface of said biological system;

(b)   obtaining a raw signal from the extracted analyte, wherein said raw signal is specifically related to the analyte;

(c)   performing a calibration step which correlates the raw signal obtained in step (b) with a measurement value indicative of the concentration of analyte present in the biological system at the time of extraction;

(d)   repeating steps (a)-(b) to obtain a series of measurement values at selected time intervals, wherein the sampling system is maintained in operative contact with the skin or mucosal surface of said biological system to provide for a continual or continuous analyte measurement; and

(e)   predicting a measurement value based on the series of measurement values using the Mixtures of Experts algorithm, where the individual experts have a linear form

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

wherein (An) is an analyte of interest, n is the number

of experts, An_i is the analyte predicted by Expert i; and w_i is a parameter, and the individual experts An_i are further defined by the expression shown as Equation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wherein, An_i is the analyte predicted by Expert i; P_j is
5   one of m parameters, m is typically less than 100; a_{ij} are coefficients; and z_i is a constant; and further where the weighting value, w_i, is defined by the formula shown as Equation (3)

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k} \right]} \qquad (3)$$

10   where e refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_i. The d_k are given by Equation 4
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$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a coefficient, P_j is one of m parameters, and where ω_k is a constant.

2.   The method of claim 1, wherein the analyte is

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extracted from the biological system in step (a) into a collection reservoir to obtain a concentration of the analyte in said reservoir.

3.   The method of claim 2, wherein the collection reservoir is in contact with the skin or mucosal surface of the biological system and the analyte is extracted using an iontophoretic current applied to said skin or mucosal surface.

4.   The method of claim 3, wherein the collection reservoir contains an enzyme that reacts with the extracted analyte to produce an electrochemically detectable signal.

5.   The method of claim 4, wherein the analyte is glucose.

6.   The method of claim 5, wherein the enzyme is glucose oxidase.

7.   The method of claim 1, wherein the prediction of step (e) is carried out using said series of two or more measurement values in an algorithm represented by the Mixtures of Experts algorithm, where the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wherein (*BG*) is blood glucose, there are three experts
(n=3) and BG_i is the analyte predicted by Expert *i*; w_i is
a parameter, and the individual Experts BG_i are further
5   defined by the expression shown as Equations 6, 7, and 8

$$BG_1 = p_1(time) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \quad (6)$$

$$BG_2 = p_2(time) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \quad (7)$$

$$BG_3 = p_3(time) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \quad (8)$$

wherein, BG_i is the analyte predicted by Expert *i*;
parameters include, *time* (elapsed time since the
sampling system was placed in operative contact with
10   said biological system), *active* (active signal), *signal*
(calibrated signal), and *BG/cp* (blood glucose value at a
calibration point); p_i, q_i, r_i, and s_i are coefficients;
and t_i is a constant; and further where the weighting
value, w_i, is defined by the formulas shown as Equations
15   9, 10, and 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

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$$W_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (10)$$

$$W_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (11)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7, and 8) that are used to determine the weights w_i, given by Equations 9, 10, and 11, and

5

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + e_1 \quad (12)$$

$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + e_2 \quad (13)$$

$$d_3 = \tau_3(time) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + e_3 \quad (14)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where e_i is a constant.

8.   The method of claim 1, wherein the prediction of step (e) is carried out using said series of two or more measurement values in an algorithm represented by the Mixtures of Experts algorithm, where the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \quad (15)$$

wherein (BG) is blood glucose, there are three experts (n=3) and BG_i is the analyte predicted by Expert i; w_i is a parameter, and the individual Experts BG_i are further defined by the expression shown as Equations 16, 17, and 18

$$BG_1 = p_1(time_c) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \quad (16)$$

$$BG_2 = p_2(time_c) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \quad (17)$$

$$BG_3 = p_3(time_c) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \quad (18)$$

wherein, BG_i is the analyte predicted by Expert i; parameters include, $time_c$ (elapsed time from a calibration of said sampling system), $active$ (active signal), $signal$ (calibrated signal), and BG/cp (blood

5   glucose value at a calibration point); p_i, q_i, r_i, and s_i are coefficients; and t_i is a constant; and further where the weighting value, w_i, is defined by the formulas shown as Equations 19, 20, and 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

10

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7, and 8) that are used to determine the weights w_i, given by Equations 19, 20, and 21, and

5

$$d_1 = \tau_1(time_c) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + \epsilon_1 \quad (22)$$

$$d_2 = \tau_2(time_c) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + \epsilon_2 \quad (23)$$

$$d_3 = \tau_3(time_c) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + \epsilon_3 \quad (24)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where ϵ_i is a constant.

10   9.   The method of either of claim 7 or claim 8, which includes further parameters for measurement values selected from the group consisting of temperature, ionophoretic voltage, and skin conductivity.

15   10.   A method for measuring blood glucose in a subject, said method comprising:
        (a)   obtaining a raw signal from a sensing apparatus, wherein said raw signal is specifically related to the glucose detected by the sensing
20   apparatus;
        (b)   performing a calibration step which correlates

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the raw signal obtained in step (a) with a measurement
value indicative of the subject's blood glucose
concentration;

    (c)   repeating step (a) to obtain a series of
5   measurement values at selected time intervals; and

    (d)   predicting a measurement value using the
Mixtures of Experts algorithm, where the individual
experts have a linear form:

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

wherein (An) is blood glucose value, n is the number of
10   experts, An_i is the blood glucose value predicted by
Expert i; and w_i is a parameter, and the individual
experts An_i are further defined by the expression shown
as Equation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wherein, An_i is the blood glucose value predicted by
15   Expert i; P_j is one of m parameters, m is typically less
than 100; a_{ij} are coefficients; and z_i is a constant; and
further where the weighting value, w_i, is defined by the
formula shown as Equation (3),

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k}\right]} \qquad (3)$$

20

where e refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_i. The d_k are given by Equation 4

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a coefficient, P_j is one of m parameters, and where ω_k is a constant.

11.   The method of claim 10, where in said Mixtures of Experts algorithm, the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wherein (BG) is blood glucose, there are three experts (n=3) and BG_i is the analyte predicted by Expert i; w_i is a parameter, and the individual Experts BG_i are further defined by the expression shown as Equations 6, 7, and 8

$$BG_1 = p_1(time) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \qquad (6)$$

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$$BG_2 = p_2(time) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \quad (7)$$

$$BG_3 = p_3(time) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \quad (8)$$

wherein, BG_i is the analyte predicted by Expert i;
parameters include, $time$ (elapsed time since the
sampling system was placed in operative contact with
said biological system), $active$ (active signal), $signal$
5   (calibrated signal), and BG/cp (blood glucose value at a
calibration point); p_i, q_i, r_i, and s_i are coefficients;
and t_i is a constant; and further where the weighting
value, w_i, is defined by the formulas shown as Equations
9, 10, and 11

10

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (11)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7, and 8) that are used to determine the weights w_i, given by Equations 9, 10, and 11, and

5

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + \epsilon_1 \quad (12)$$

$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + \epsilon_2 \quad (13)$$

$$d_3 = \tau_3(time) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + \epsilon_3 \quad (14)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where ϵ_i is a constant.

12. The method of claim 10, where in said Mixtures
10   of Experts algorithm, the individual experts have a

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linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (15)$$

5   wherein (BG) is blood glucose, there are three experts
(n=3) and BG_i is the analyte predicted by Expert i; w_i is
a parameter, and the individual Experts BG_i are further
defined by the expression shown as Equations 16, 17, and
18

$$BG_1 = p_1(time_c) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \quad (16)$$

$$BG_2 = p_2(time_c) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \quad (17)$$

$$BG_3 = p_3(time_c) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \quad (18)$$

10 wherein, BG_i is the analyte predicted by Expert i;
parameters include, $time_c$ (elapsed time from a
calibration of said sampling system), $active$ (active
signal), $signal$ (calibrated signal), and BG/cp (blood
glucose value at a calibration point); p_i, q_i, r_i, and s_i
15 are coefficients; and t_i is a constant; and further where
the weighting value, w_i, is defined by the formulas shown
as Equations 19, 20, and 21

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$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (19)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7, and 8) that
5   are used to determine the weights w_i, given by Equations 19, 20, and 21, and

$$d_1 = \tau_1 (time_c) + \beta_1 (active) + \gamma_1 (signal) + \delta_1 (BG|cp) + \epsilon_1 \quad (22)$$

$$d_2 = \tau_2 (time_c) + \beta_2 (active) + \gamma_2 (signal) + \delta_2 (BG|cp) + \epsilon_2 \quad (23)$$

$$d_3 = \tau_3 (time_c) + \beta_3 (active) + \gamma_3 (signal) + \delta_3 (BG|cp) + \epsilon_3 \quad (24)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where ϵ_i is
10   a constant.

13. The method of either claim 11 or claim 12, wherein the sensing apparatus is a near-IR spectrometer.

14. The method of either claim 11 or claim 12, wherein the sensing means comprises a biosensor having an electrochemical sensing element.

15. A monitoring system for continually or continuously measuring an analyte present in a biological system, said system comprising, in operative combination:

(a) sampling means for continually or continuously extracting the analyte from the biological system, wherein said sampling means is adapted for extracting the analyte across a skin or mucosal surface of said biological system;

(b) sensing means in operative contact with the analyte extracted by the sampling means, wherein said sensing means obtains a raw signal from the extracted analyte and said raw signal is specifically related to the analyte; and

(c) microprocessor means in operative communication with the sampling means and the sensing means, wherein said microprocessor means (i) is used to control the sampling means and the sensing means to obtain a series of raw signals at selected time intervals during a continual or continuous measurement period, (ii) correlate the raw signals with measurement values indicative of the concentration of analyte present in the biological system, and (iii) predict a

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measurement value using the Mixtures of Experts algorithm, where the individual experts have a linear form

$$An = \sum_{i=1}^{n} An_i w_i \qquad (1)$$

wherein (An) is an analyte of interest, n is the number of experts, An_i is the analyte predicted by Expert i; and w_i is a parameter, and the individual experts An_i are further defined by the expression shown as Equation (2)

$$An_i = \sum_{j=1}^{m} a_{ij} P_j + z_i \qquad (2)$$

wherein, An_i is the analyte predicted by Expert i; P_j is one of m parameters, m is typically less than 100; a_{ij} are coefficients; and z_i is a constant; and further where the weighting value, w_i, is defined by the formula shown as Equation (3)

$$w_i = \frac{e^{d_i}}{\left[\sum_{k=1}^{n} e^{d_k} \right]} \qquad (3)$$

where e refers to the exponential function and the d_k (note that the d_i in the numerator of Equation 3 is one of the d_k) are a parameter set analogous to Equation 2 that is used to determine the weights w_i. The d_k are given by Equation 4

$$d_k = \sum_{j=1}^{m} \alpha_{jk} P_j + \omega_k \qquad (4)$$

where α_{jk} is a coefficient, P_j is one of m parameters, and where ω_k is a constant.

16.   The monitoring system of claim 15, wherein the sampling means includes one or more collection reservoirs for containing the extracted analyte.

17.   The monitoring system of claim 16, wherein the sampling means uses an iontophoretic current to extract the analyte from the biological system.

18.   The monitoring system of claim 17, wherein the collection reservoir contains an enzyme that reacts with the extracted analyte to produce an electrochemically detectable signal.

19.   The monitoring system of claim 18, wherein the analyte is glucose and the enzyme is glucose oxidase.

20.   A monitoring system for measuring blood glucose in a subject, said system comprising, in operative combination:

(a)   sensing means in operative contact with the subject or with a glucose-containing sample extracted from the subject, wherein said sensing means obtains a raw signal specifically related to blood glucose in the subject; and

(b) microprocessor means in operative communication with the sensing means, wherein said microprocessor means (i) is used to control the sensing means to obtain a series of raw signals at selected time

5 intervals, (ii) correlates the raw signals with measurement values indicative of the concentration of blood glucose present in the subject, and (iii) predicts a measurement value at a further time interval using the Mixtures of Experts algorithm, where the individual

10 experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (5)$$

wherein (BG) is blood glucose, there are three experts (n=3) and BG_i is the analyte predicted by Expert i; w_i is

15 a parameter, and the individual Experts BG_i are further defined by the expression shown as Equations 6, 7, and 8

$$BG_1 = p_1(time) + q_1(active) + r_1(signal) + s_1(BG|cp) + t_1 \qquad (6)$$

$$BG_2 = p_2(time) + q_2(active) + r_2(signal) + s_2(BG|cp) + t_2 \qquad (7)$$

$$BG_3 = p_3(time) + q_3(active) + r_3(signal) + s_3(BG|cp) + t_3 \qquad (8)$$

wherein, BG_i is the analyte predicted by Expert i;

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parameters include, *time* (elapsed time since the
sampling system was placed in operative contact with
said biological system), *active* (active signal), *signal*
(calibrated signal), and *BG/cp* (blood glucose value at a
calibration point); p_i, q_i, r_i, and s_i are coefficients;
and t_i is a constant; and further where the weighting
value, w_i, is defined by the formulas shown as Equations
9, 10, and 11

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (9)$$

$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (10)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (11)$$

10

where e refers to the exponential function and d_i is a
parameter set (analogous to Equations 6, 7, and 8) that
are used to determine the weights w_i, given by Equations
9, 10, and 11, and

$$d_1 = \tau_1(time) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + \epsilon_1 \quad (12)$$

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$$d_2 = \tau_2(time) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + e_2 \quad (13)$$

$$d_3 = \tau_3(time) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + e_3 \quad (14)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where e_i is a constant.

21.   A monitoring system for measuring blood
5   glucose in a subject, said system comprising, in operative combination:
(a)   sensing means in operative contact with the subject or with a glucose-containing sample extracted from the subject, wherein said sensing means obtains a
10   raw signal specifically related to blood glucose in the subject; and
(b)   microprocessor means in operative communication with the sensing means, wherein said microprocessor means (i) is used to control the sensing
15   means to obtain a series of raw signals at selected time intervals, (ii) correlates the raw signals with measurement values indicative of the concentration of blood glucose present in the subject, and (iii) predicts a measurement value at a further time interval using the
20   Mixtures of Experts algorithm, where the individual experts have a linear form

$$BG = w_1 BG_1 + w_2 BG_2 + w_3 BG_3 \qquad (15)$$

wherein (BG) is blood glucose, there are three experts (n=3) and BG_i is the analyte predicted by Expert i; w_i is a parameter, and the individual Experts BG_i are further

5   defined by the expression shown as Equations 16, 17, and 18

$$BG_1 = p_1 (time_c) + q_1 (active) + r_1 (signal) + s_1 (BG|cp) + t_1 \quad (16)$$

$$BG_2 = p_2 (time_c) + q_2 (active) + r_2 (signal) + s_2 (BG|cp) + t_2 \quad (17)$$

$$BG_3 = p_3 (time_c) + q_3 (active) + r_3 (signal) + s_3 (BG|cp) + t_3 \quad (18)$$

wherein, BG_i is the analyte predicted by Expert i; parameters include, $time_c$ (elapsed time from a calibration of said sampling system), $active$ (active

10   signal), $signal$ (calibrated signal), and BG/cp (blood glucose value at a calibration point); p_i, q_i, r_i, and s_i are coefficients; and t_i is a constant; and further where the weighting value, w_i, is defined by the formulas shown as Equations 19, 20, and 21

$$w_1 = \frac{e^{d_1}}{e^{d_1} + e^{d_2} + e^{d_3}} \qquad (19)$$

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$$w_2 = \frac{e^{d_2}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (20)$$

$$w_3 = \frac{e^{d_3}}{e^{d_1} + e^{d_2} + e^{d_3}} \quad (21)$$

where e refers to the exponential function and d_i is a parameter set (analogous to Equations 6, 7, and 8) that

5 are used to determine the weights w_i, given by Equations 19, 20, and 21, and

$$d_1 = \tau_1(time_c) + \beta_1(active) + \gamma_1(signal) + \delta_1(BG|cp) + \epsilon_1 \quad (22)$$

$$d_2 = \tau_2(time_c) + \beta_2(active) + \gamma_2(signal) + \delta_2(BG|cp) + \epsilon_2 \quad (23)$$

$$d_3 = \tau_3(time_c) + \beta_3(active) + \gamma_3(signal) + \delta_3(BG|cp) + \epsilon_3 \quad (24)$$

where τ_i, β_i, γ_i and δ_i are coefficients, and where ϵ_i is

10 a constant.

22. The monitoring system of either claim 20 or claim 21, which includes further parameters for raw signals selected from the group consisting of

temperature, ionophoretic voltage, and skin
conductivity.

23.   The monitoring system of either claim 20 or
5   claim 21, wherein the sensing means comprises a
biosensor having an electrochemical sensing element.

24.   The monitoring system of either claim 20 or
claim 21, wherein the sensing means comprises a near-IR
10   spectrometer.